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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional): 2473.0030005/PAJ/LMB

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" [37 CFR 1.8(a)]

on _____

Signature _____

Typed or printed name _____

Application Number	Filed
09/357,737	July 19, 1999

First Named Inventor: Alessandro SETTE

Art Unit	Examiner
1644	Schwadron, Ronald B.

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- [ ] applicant/inventor.
- [ ] assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- [ ] attorney or agent of record. Registration number _____
- [X] attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 57,772

Lori M. Brandes
Signature

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April 12, 2010
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

[X] *Total of 1 forms are submitted.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 9669
SETTE *et al.*	Art Unit: 1644
Appl. No.: 09/357,737	Examiner: Schwadron, Ronald B.
Filed: July 19, 1999	Atty. Docket: 2473.0030005/PAJ/LMB
For: **Inducing Cellular Immune Responses to Hepatitis C Virus Using Peptide and Nucleic Acid Compositions**	

Arguments to Accompany the Pre-Appeal Brief Request for Review

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Mail Stop AF

Sir:

Applicants submit the following Arguments along with a Pre-Appeal Brief Request for Review (Form PTO/SB/33). A Notice of Appeal is concurrently filed.

The Examiner rejected claims 166, 168, 170, 177 and 247 under 35 U.S.C. § 103(a) as allegedly unpatentable over Chien (U.S. Pat. No. 6,150,087), in view of Berzofsky (U.S. Pat. No. 5,980,899) and Guo (*Nature 360*:364-366 (1992)) in the December 10, 2009 Final Office Action. The Examiner's rejection was legally and factually deficient because the Examiner failed to establish *prima facie* obviousness and to adequately address the evidence of unexpected results.

At page 3, line 4 of the Final Office Action, the Examiner acknowledged "Chien et al. do not teach the peptide of claim 166/168" (GVAGALVAFK). However, the Examiner alleged that the claims are obvious "...because Ch[i]en et al. teach an immunogenic HCV [hepatitis C virus] peptide containing GVAGALVAFK..." (page 3, lines 11-12), and that one of ordinary skill in the art would have arrived at the claimed peptide by screening the peptide of Chien "...because Berzofsky et al. teach that it is desirable to identify CTL epitopes found in HCV and Guo et al. teach that CTL recognize viral peptides complexed with MHC and that peptides which bind HLA-Aw68 generally are 9 to 11 amino acids with a V at P2 (position 2) and a K at the c-terminal position" (page 3, lines 15-21). The Examiner further alleged that in a post-*KSR* (*KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398 (2007)) universe, "...if a technique has been used to

improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." Final Office Action at page 3, lines 30-33, quoting *KSR*.

Chien in view of Berzofsky and Guo fail to disclose or render obvious the inventions of any one of claims 166, 168, 170, 177 and 247. USPTO guidance and case law precedent indicate that in order for a claimed result to be obvious in view of a combination of known options, the result must be *predictable*. *See* MPEP 2143; *KSR*, 550 U.S. 398 (2007). In the Final Office Action, the Examiner relies on the rationale provided in *KSR* and explained in MPEP 2143(C) related to the use of an allegedly known technique to improve similar devices in the same way. Specifically, MPEP 2143(C) indicates that when using this rationale, USPTO personnel *must* articulate, among other things: (i) that one of ordinary skill in the art could have applied the known technique in the *same* way to the claimed device with a *predictable* result; and (ii) additional findings based on the *Graham* factual inquiries (*e.g.*, unexpected results) in view of the facts of the case. Applicants assert the Examiner has failed to articulate these points and has therefore failed to establish a *prima facie* case of obviousness.

The Examiner has not established that the claimed invention would have been *predictable* in view of the cited references. Chien discloses over 180 different HCV peptides ranging in size up to 70 amino acids in length and spanning a sequence that is nearly 3000 amino acids in length. *See* Chien at Figures 1-90; *see also* pages 5-7 of the February 10, 2010 Amendment and Reply. While Applicants do not disagree that Chien discloses a 50 amino acid peptide comprising the elected 10 amino acid peptide (AA1850-AA1900), Chien does not provide any guidance as to which of the voluminous disclosed peptides would be best suited to obtain an immunogenic HCV sequence. Therefore, there are potentially hundreds, or even thousands, of different immunogenic epitopes that could be selected within this large sequence of Chien. The Examiner is applying hindsight reasoning in selecting one particular peptide of those disclosed in Chien to use as a

starting point because, without the knowledge of the elected peptide being an effective CTL epitope, nothing in Chien would lead to the elected peptide.

This proposition is supported by the Declaration of Dr. Alessandro Sette (*i.e.*, one of ordinary skill in the relevant art), filed as Exhibit E of the September 25, 2009 Amendment and Reply ("Sette Declaration"). It is Dr. Sette's opinion that "one of ordinary skill in the art, considering the art related to CTL peptide motifs as a whole, would not be able to narrow down the huge number of equally reasonable HCV CTL epitope candidates to a more *finite number of identifiable, predictable solutions*." Sette Declaration at ¶ 36 (emphasis added); *see also* pages 8-10 of the February 10, 2010 Amendment and Reply. Thus, as stated by Dr. Sette, Chien offers no further suggestion as to how to narrow down the vast number of possible peptides that could be generated by the brute force screening method proposed by the Examiner to predictably arrive at one, or even a reasonable number, of possible immunogenic peptides. Sette Declaration at ¶ 15.

Further, according to Dr. Sette, the Examiner has arbitrarily focused on only one of the potential HLA-Aw68 peptide motifs disclosed in Guo. Sette Declaration at ¶ 23. Guo discloses that HLA-Aw68 motifs are also characterized by a V at P2 and an R at the C-terminus; and a T at P2 and an R at the C-terminus. *See id.*; Guo at page 364, Table 1. Additional motifs were also known at the time the present application was filed and include an HLA-B27 motif (Jardetzky *et al.*, Exhibit B of the September 25, 2009 Amendment and Reply); an HLA-A2.1 motif (Hunt *et al.*, *Id.* at Exhibit C); and HLA-B35 and -B37 motifs (Falk *et al.*, *Id.* at Exhibit D). In Dr. Sette's view, one attempting to identify an HCV epitope recognized by T cells would have considered all known motifs, including those of Jardetzky, Hunt and Falk, and not just the motifs disclosed in Guo. Sette Declaration at ¶ 34. However, even assuming that one would consider Chien and Guo alone, the combination of Chien and Guo would still result in nearly 60 possible CTL peptide candidates. Sette Declaration at ¶ 24; *see also* pages 8-9 of the September 25, 2009 Amendment and Reply. As discussed by Dr. Sette, one of ordinary skill in the art would have no further

guidance from Chien, Berzofsky or Guo to narrow down the 60 possibilities to a fewer number of peptides, and certainly would have no information to select the elected peptide of the claims. Sette Declaration at ¶ 35; *see also* page 11 of the September 25, 2009 Amendment and Reply. As further support, Applicants have provided the Yewdell, Eisenlohr and DelVal references for the proposition that it is difficult to identify exactly which specific peptides are capable of inducing an immune response within a given longer sequence. *See* pages 11-12 of the February 10, 2010 Amendment and Reply.

In a post-*KSR* case, *Takeda Chem. Indust., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007), the Federal Circuit elaborated on the issue of obviousness where the prior art disclosed a large number of possible solutions. *See Takeda*, 492 F.3d at 1359; *see also* pages 5-6 of the February 10, 2010 Amendment and Reply. Applicants maintain that the present case is similar to *Takeda* because the cited references, at best, provide an extremely large number of epitopes upon which one can apply certain screening criteria, with no guarantee that an immunogenic CTL epitope will be identified.

Moreover, there is insufficient rationale for relying on Berzofsky and Guo to cure the deficiencies of Chien. The elected peptide is neither discussed, nor described in Berzofsky or Guo. While Berzofsky generally describes other regions of HCV (*see* Abstract), it does not provide any guidance with regard to which specific regions of HCV necessarily contain good targets for CTL, nor does it contain any guidance to identify the elected peptide. Also, the peptides of Applicants' claimed invention are determined using *different* techniques that do not rely on the amphipathicity algorithm of Berzofsky. *See* Abstract. Guo does not remedy the deficiencies of Chien or Berzofsky because it only generally describes how CTL recognize viral peptides complexed with MHC and certain structural features of such peptides. *See* page 364. Accordingly, Berzofsky and Guo do not establish that one of ordinary skill in the art could have applied a known technique in the *same way* to *predictably* arrive at the elected peptide.

Thus, in view of the cited art, one of ordinary skill in the art would not *predictably* arrive at the elected peptide and would not have applied known techniques in the *same way* to arrive at the elected peptide. As such, the Examiner has not provided the requisite rationale for the obviousness rejection and therefore the cited references do not render the claims obvious.

Moreover, the Examiner has not adequately addressed the evidence of unexpected results of record, as required under MPEP 2143(c). As evidence of unexpected results, and further evidence of unpredictability, the elected peptide was shown to exhibit the strongest CTL-inducing response in transgenic mice as compared to any of the other peptides listed in Table XXIII of the specification and as compared to the over 400 other peptides sharing the same A3 motif. *See* Table XVI and Sette Declaration at ¶ 40. As such, one of ordinary skill in the art would *not* have expected the elected peptide to have higher affinity and immunogenicity than others sharing the same motif. Sette Declaration at ¶ 40. This criticality of the HLA binding affinity is also disclosed in the specification, for example, at paragraphs [0096]-[0097]. In view of the improved binding properties of the elected peptide as compared to over 400 other peptides sharing the same motif, and in view of the significantly greater CTL induction generated as compared to numerous other peptides sharing the same motif, Applicants assert that evidence of unexpected results is present and thus renders the elected peptide non-obvious in view of the cited references.

For at least these reasons, the Examiner has failed to establish a *prima facie* case of obviousness. Accordingly, Applicants respectfully request that the outstanding rejection be withdrawn and the claims allowed.

Respectfully submitted,
STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

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